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STEREOSELECTIVITY AT BENZYLIC CARBON

FLAVANOIDS—V[1]. SYNTHESIS OF *TRANS*-4-ACETAMIDOFLAVANS

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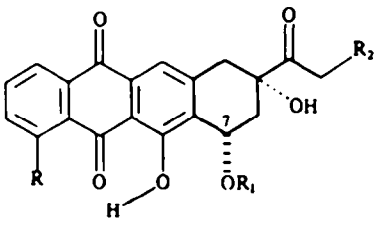
Abstract—Some reactions of 4-substituted flavans have been studied. 4-Chloro/bromo derivatives react under neutral conditions with phthalimide and acetonitrile leading to displacement of axial halogen by nitrogen with inversion. In contrast, irrespective of the stereochemistry, 4-hydroxy-derivatives react under acidic or basic conditions leading to axial attack by the nucleophiles $SOCl_2$, PCl_3, PCl_5, $SOBr_2$, PBr_3, PBr_5, acetonitrile and water, evidently through the intermediate formation of a benzylic carbocation.

In contrast with the knowledge of the steric course of various reactions in acyclic or alicyclic systems, similar information on the reactions at the benzylic carbon which are part of cyclic systems (flavans, etc.) is rather scanty. This area is becoming increasingly important especially with the advent of anthracycline antitumor antibiotics with the general aglycone structure **1**. Particular difficulties have been encountered for the introduction of an OH group at C-7 by the stereospecific reduction of the C-7 keto group or oxidation of the C-7 benzylic methylene[2] and hence the study of the reactions at the benzylic carbon is of relevance.



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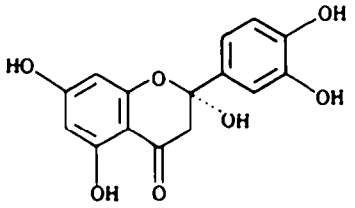
The flavan nucleus having a bulky C-2 aryl substituent and only one benzylic carbon C-4 appeared to be an ideal substrate and is more attractive because a 2-hydroxyflavanone derivative **2** structurally similar to 7-keto anthracyclines has also been isolated from natural sources.[3] Our studies involve various reactions at the benzylic carbon C-4 of a flavan nucleus with an ultimate aim at the synthesis of isomeric 4-aminoflavans extendable to anthracyclines. Two groups of workers[4] have been engaged in this problem and 4-aminoflavan obtained by Bognár *et al.*[5] has been subsequently shown to be the *cis* isomer by ^{1}H-NMR studies of the derived 4-phthalimidoflavan.[6] Various approaches for the synthesis of *trans*-4-aminoflavan by the former workers proved unsuccessful.[7] We now report the first synthesis of two pairs of isomeric 4-acetamidoflavans and various routes used for this show a specific pattern of substitution at the benzylic carbon under acidic, basic and neutral conditions. Following the route established in the alicyclic series viz. *cis*-alcohol to *cis*-tosylate or mesylate to *trans*-azide to *trans*-amine,[8] *cis*-4-hydroxyflavan **3a** was treated with mesyl chloride and pyridine. Instead of the expected *cis*-4-mesyloxyflavan **3b** the reaction gave *trans*-4-hydroxyflavan **4a**. To verify the intermediacy of **3b** and its subsequent hydrolysis with inversion to **4a** the reaction when repeated gave instead of **3b** a different product with no OH group (IR check), which contained chlorine, and with aqueous pyridine at room temperature it gave flav-3-ene.[9] It was identified as 4-chloroflavan **5**. Hydrolysis of **5** to **4a** was better at 0°



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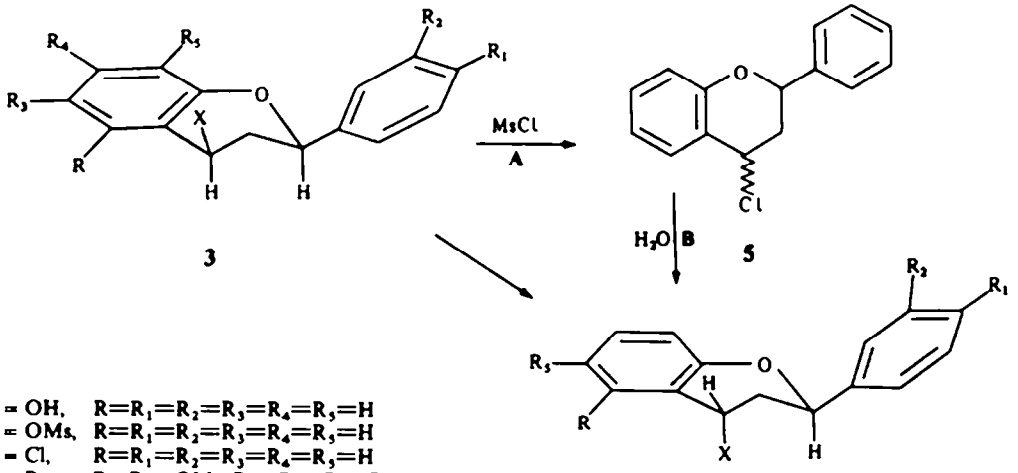
with aqueous DMSO or DMF and Li_2CO_3. No proof was available as to whether in the formation of **5** also **3b** is an intermediate because if formed it would have been susceptible to the nucleophilic attack by Cl^- present.[10] Formation of **4a** from **3a** via **5** involves only one inversion (Fig. 1) either at **A** or **B**. At the outset it appeared that of the two reactions, **A** is more likely to be S_Ni than **B** and if so, reaction **B** involving base hydrolysis would be of S_N2 type and in support **5** showed IR bands at 740 and 780 cm^{-1} corresponding to equatorial C—Cl stretching,[11] suggesting this to be the *cis* isomer **3c**. Similarly 4-bromo-4',5-dimethoxy- and 4-bromo-3',4',5-trimethoxyflavans synthesized from the related *cis*-4-hydroxyflavans using PBr_3 have been considered by other workers as the *cis* isomers (C-4 equatorial) **3d** and **3e**, and their alkaline hydrolysis to give the related *trans*-4-hydroxyflavans **4b** and **4c** was claimed to be an S_N2 displacement and the initial conversion of OH to Br is with retention of stereochemistry (S_Ni process at **A**).[12] These apparent S_Ni reactions are contrary to the well established nucleophilic displacements with inversion, unless contrary to the well established stable conformation of 4-substituted flavans with the C-2 aryl group equatorial, the expected inversion at **A** is accompanied by a conformational change and the stable conformation of the resulting *trans*-4-chloroflavan has the bulky C-4 chlorine equatorial and the C-2 aryl group



3 5 4

a X = OH, R=R₁=R₂=R₃=R₄=R₅=H
b X = OMs, R=R₁=R₂=R₃=R₄=R₅=H
c X = Cl, R=R₁=R₂=R₃=R₄=R₅=H
d X = Br, R=R₁=OMe, R₂=R₃=R₄=R₅=H
e X = Br, R=R₁=R₂=OMe, R₃=R₄=R₅=H
f X = OH, R=R₁=R₂=R₄=R₅=H, R₃=CH₃
g X = OH, R=R₂=R₄=R₅=H, R₁=OCH₃, R₃=CH₃
h X = OH, R=R₄=R₅=H, R₁=R₂=OMe, R₃=CH₃
i X = OH, R=R₃=R₄=R₅=H, R₁=R₂=OMe
j X = OH, R₁=R₂=R₄=R₅=OMe, R=R₃=H
k X = OTs, R to R₅=H
l X = OTs, R=R₁=R₂=R₄=R₅=H, R₃=CH₃

a X = OH, R=R₁=R₂=R₅=H
b X = OH, R=R₁=OMe, R₂=R₅=H
c X = OH, R=R₁=R₂=OMe, R₅=H
d X = Cl, R=R₁=R₂=R₅=H
e X = Br, R=R₁=R₂=R₅=H

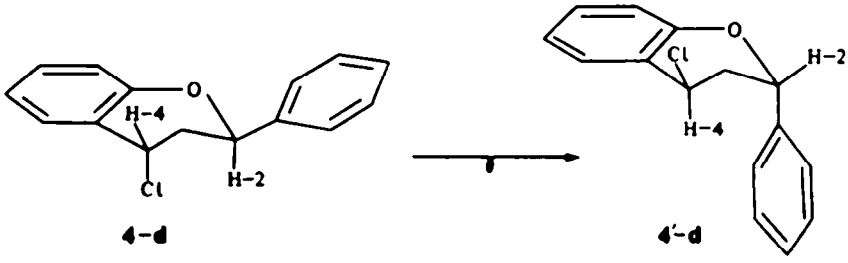
Fig. 1.

axial as in 4'd† (Fig. 2) to accommodate the IR spectral data. This was settled by examination of the ^{1}H-NMR spectrum of 5 which clearly proved this to be the *trans* isomer 4d or 4'd having the signal for H-4 in 4d or for H-2 in 4'd at δ 5.12 as a narrow triplet (overlapping double doublet) with a smaller total spread ($J_{e,e+e,e}$ = 8 Hz) as compared to the quartet from H-2 in 4d or from H-4 in 4'd at δ 5.41 ($J_{a,a+a,e}$ = 16 Hz) due to coupling with one equatorial and one axial proton, respectively.[6] In the ^{1}H-NMR spectrum of the known 4-bromoflavan[13] in $CDCl_3$ the signals for H-2 and H-4 were overlapping (δ 5.43–5.76) but the coupling constants (overlapping narrow triplet and a broad quartet) suggested the *trans* isomer;[7] the assignment was confirmed by examining the spectrum in benzene when two well separated signals, one with larger spread ($J_{a,e+a,a}$ = 18 Hz) than the other ($J_{a,a+e,e}$ = 8 Hz), were observed. Similar studies established the stereochemistry of five 4-halogenoflavan derivatives as the *trans* isomers 4 (or 4')-f, -g, -h,[12] -i and -j (spectra run in C_6D_6 wherever necessary).

Of the two possible conformations 4d and 4'd for *trans*-4-chloroflavan the preferred conformation was arrived at by ^{13}C-NMR studies. The ^{13}C-NMR spectrum of *trans*-4-chloroflavan showed the signal for C-2 at 73.123 ppm as compared to that at 73.124 ppm for C-2 in *trans*-hydroxyflavan 4a in contrast with the one at 77.023 ppm for the *cis* isomer 3a (confirmed by taking new proton-noise decoupled and single frequency off resonance decoupled spectral measurements on a JEOL-Fx-100 instrument). The upfield shift of 3.90 ppm, attributed to the heteroatom γ-gauche effect, defined the axial nature of chlorine at C-4, as the γ-*trans* effect of chlorine on the chemical shift of C-2 is negligible (0.2 ppm)[14] and hence the conformation of *trans*-4-chloroflavan is as 4d and not as 4'd suggested by IR studies. Similar ^{13}C-NMR studies on 4-bromo-, 4-chloro-6-methyl- and 4-bromo-6-methylflavans confirmed their conformation as 4e, 4f and 4g, respectively (Table 1), and the literature assignment of 3e[12] has to be reversed as 4h.

The formation of 4a from 3a via 5, i.e. 4d was generalized by the synthesis of five more compounds 4k to 4o from the *cis* alcohols 3f, 3g, 3h, 3i and 3j via the

† For clarity the conformational inversion of 4d to 4'd is represented by epimerizing both the C-2 and C-4 substituents, i.e. 4'd is the enantiomer of 4d and this is of no consequence as we are dealing with racemic compounds.



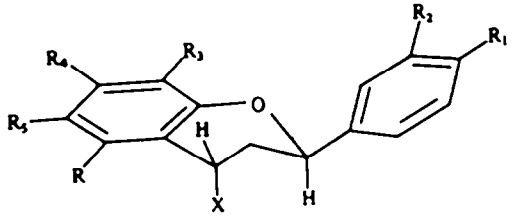
4-d 4'-d

Fig. 2.

Table 1. ^{13}C-NMR values for 4-substituted flavans

Compound	3a	4a	4d	4e	4f	4g
C-2	77.00	73.00	73.18	74.00	73.14	73.40
C-4	65.80	63.90	53.66	45.76	53.98	46.10

trans-4-chloroflavans which were not isolated. Similarly *trans*-4-bromoflavans **4e**, **4g**, **4i** and **4j** treated with aqueous Li_2CO_3–DMF furnished in high yields the *trans*-4-hydroxyflavans **4a**, **4k**, **4l** and **4p**, respectively. Moreover *cis*-4-hydroxy-3′,4′,7-trimethoxyflavan with PBr_3 did not give the related *trans*-4-bromoflavan; the only product isolated was the *trans* alcohol **4q**. Compound **4l** by this route[6] has the m.p. 135–136°. This compound prepared by Al–Hg[15] and $Al(O—Pr^i)_3$[16] reduction of the related flavanone melted at 127–128° as reported, and it could not be improved by crystallization. The ^{1}H-NMR spectra of the two samples were indistinguishable and so the low m.p. was attributed to contamination by a small amount of the *cis* isomer due to epimerization by $Al(O—Pr^i)_3$.[17] Comparison of the IR spectrum of an artificial 90:10 mixture of pure *trans* isomer, m.p. 135°, and the *cis* isomer, m.p. 137–138°, was found to be almost identical with the sample with m.p. 127–128°. The compound **4k** obtained by the above route melted at 92° (acetate m.p. 110°), while this has been reported[18] as a liquid b.p. 86–87°/4 mm when obtained from 6-methylflavan by $Pb(OAc)_4$ oxidation and subsequent hydrolysis. On repeating this preparation the oxidation product (containing much starting material) on chromatographic purification furnished *trans*-4-acetoxy-6-methylflavan, m.p. 110°, in 9% yield. This on alkaline hydrolysis gave **4k**.



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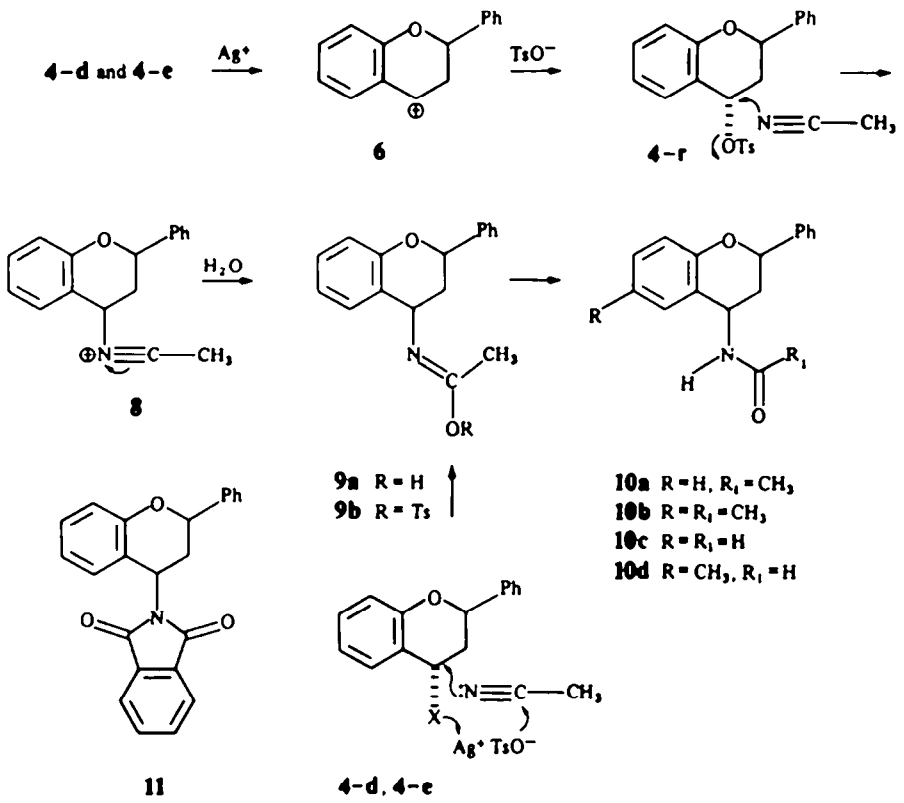
Thus formation of 4-halogenoflavans from *cis*-4-hydroxyflavans involves inversion while the hydrolysis is with retention possibly via the incipient formation of a benzyl carbocation (S_N1 process) *vide infra* and subsequent axial approach of the nucleophiles to achieve efficient orbital overlap,[19] and these reactions provide a new high purity, high yield synthesis of *trans*-4-hydroxyflavans.

An alternative synthesis of *cis*-4-tosyloxyflavan **3k** for its conversion to *trans*-azide and *trans*-amine was envisaged via the now readily available *trans*-4-halogenoflavans by substitution of the halogen by a tosyloxy group with inversion using silver tosylate (cf. ref. 20). Initial reaction of AgOTs with **4e** in dioxan was unsuccessful but in acetonitrile this as well as **4d** furnished an S-free N-containing compound proved to be *cis*-4-acetamidoflavan (ν_{CO} = 1660 cm^{-1}; ν_{NH} = 3290 cm^{-1}) **10a** identical with the earlier reported 4-acetamidoflavan[5] later shown to be the *cis* isomer.[6] Similarly **4f** and **4g** with AgOTs–CH_3CN gave *cis*-4-acetamido-6-methylflavan **10b** identical with that obtained from 6-methylflavanone by oximation, subsequent $LiAlH_4$ reduction and acetylation. In its ^{1}H-NMR spectrum ($CDCl_3$) the overlapping H-4 multiplet and H-2 quartet signals were simplified into two well separated quartets ($J_{4a,3a+4a,3e}$ = 17 Hz; $J_{2a,3a+2a,3e}$ = 12 Hz) by D_2O exchange, possible only after addition of Et_3N, and defined the stereochemistry as *cis*. This unusual formation of **10a** could involve initial formation of the benzyl carbocation **6** under Ag^+ catalysis, subsequent axial approach of the tosylate ion giving the intermediate *trans*-4-tosyloxyflavan **4r**, followed by nucleophilic displacement with inversion by the acetonitrile nitrogen lone pair and hydrolysis of the resulting ammonium or iminocarbonium ion **8** to the enol **9a** yielding **10a** (Scheme 1).

To check this *trans*-4-tosyloxyflavan **4r** was required. In contrast with the unsuccessful tosylation and mesylation of *cis* alcohol **3a**, the *trans* isomers **4a** and **4k** with TsCl, phase transfer catalyst (benzyl cetyl dimethyl ammonium chloride) and KOH or K_2CO_3 under wet or dry conditions furnished *trans*-4-tosyloxyflavans **4r** and **4s**, respectively (see Table 2 for ^{1}H-NMR values). **3f** under these conditions gave an inseparable 9:11 mixture of **4s** and *cis*-6-methyl-4-tosyloxyflavan **3l** [^{1}H-NMR ($CDCl_3$): δ 5.48 (1H,

Table 2. ^{1}HNMR values for *trans*-4-substituted flavans (**4**)

Substituent / Compound	X	R	R_1	R_2	R_3	R_4	R_5	H-2 δ (J, Hz)	H-4 δ (J, Hz)
4d	Cl	H	H	H	H	H	H	5.42 (14)	5.12 (6)
4e	Br	H	H	H	H	H	H	5.76 (18)	5.43 (8)
4f	Cl	H	H	H	H	H	CH_3	5.43 (14)	5.30 (6)
4g	Br	H	H	H	H	H	CH_3	5.53 (14)	5.03 (6)
4h	Br	OCH_3	OCH_3	OCH_3	H	H	H	5.94 (14)	5.77 (5)
4i	Br	H	OCH_3	H	H	H	CH_3	4.52 (14)	4.97 (6)
4j	Br	H	H	H	Br	H	CH_3	5.56 (14)	5.28 (6)
4k	OH	H	H	H	H	H	CH_3	5.06 (14)	4.50 (5)
4l	OH	H	OCH_3	H	H	H	CH_3	5.16 (14)	4.75 (6)
4m	OH	H	OCH_3	OCH_3	H	H	CH_3	5.17 (14)	4.75 (6)
4n	OH	H	OCH_3	OCH_3	H	H	H	5.23 (14)	4.82 (6)
4o	OH	H	OCH_3	OCH_3	OCH_3	OCH_3	H	5.30 (14)	4.80 (6)
4p	OH	H	H	H	Br	H	CH_3	5.35 (14)	4.74 (5)
4q	OH	H	OCH_3	OCH_3	H	OCH_3	H	5.21 (15)	4.79 (6)
4r	OTs	H	H	H	H	H	H	5.37 (14)	4.68 (6)
4s	OTs	H	H	H	H	H	CH_3	5.40 (13)	4.75 (6)



Scheme 1.

$J_{2a,3a+2a,3e}$ = 14 Hz, H-2), 5.11 (dd, $J_{4a,3a+4a,3e}$ = 23 Hz, H-4)]. However **4r** was unreactive towards acetonitrile and this suggested an alternative mechanism involving a rearside attack of acetonitrile with simultaneous departure of the halide ion assisted by Ag^+ with a concomitant attack of the tosylate ion giving the *cis*-imino enol tosylate **9b** which on hydrolysis would furnish **10a**. This was supported by the isolation of an unstable intermediate containing sulphur, most probably **9b**, which gave **10a** on hydrolysis.

These results indicate that in contrast to the basic conditions, under neutral conditions nucleophilic displacement of Br by nitrile nitrogen has taken place with inversion. This is a novel variation of the well known Ritter reaction discussed later.

In support of the above generalization **4e** with K-phthalimide in DMF furnished *cis*-4-phthalimidoflavan.[6] It follows that if one has *cis*-4-halogenoflavans, either AgOTs–CH_3CN or K-phthalimide–DMF treatment would yield *trans*-4-aminoflavan derivatives. If the well established displacement with inversion of OH by Cl or Br using P halides and the S_Ni reaction of alcohols with S oxyhalides with retention[21] is applicable at benzylic carbon as well then *cis* alcohol **3a** with $SOCl_2$ or $SOBr_2$ or the now readily available *trans* isomer **4a** with PCl_3, PCl_5, $POCl_3$, PBr_3 and PBr_5 would give *cis*-4-halogenoflavans with retention in the former and with inversion in the latter cases. However both **3a** and **4a** with all these reagents gave only the *trans* isomers **4d** and **4e** identified by m.ps, mixed m.ps, IR, ^{1}H-NMR and ^{13}C-NMR spectral studies. This could be accounted for only by the consideration that in contrast with the reactions of **4d** and **4e** under neutral conditions, acidic conditions lead to a stable benzyl carbocation **6** followed by axial attack of the nucleophilic halide. It seems that acid as weak as thiophenol brings about the cleavage of the benzyl C—O linkage in procyanidin dimers giving axial substitution via the S_Ni process.[22]

It was hoped that similar to 4-t-butylcyclohexanone,[23] reductive amination of flavanone by the Leuckart reaction would give the *trans*-4-N-formylaminoflavan along with the *cis* isomer. In the event the reaction furnished *cis*-4-N-formylaminoflavan **10c** as the only isolable product which was reduced to *cis*-4-N-methylaminoflavan **12a**. In the reaction with 6-methylflavanone the resulting product showed in its ^{1}H-NMR spectrum the presence of two formyl protons at δ 8.2 and 8.3, confirmed by two CO carbon signals at 159.8 and 160.9 ppm in its ^{13}C-NMR spectrum indicating the formation of isomeric 4-N-formylamino-6-methylflavans **10d** and **13a** of which **10d** was synthesized by formylation of the *cis*-4-amino-6-methylflavan and further reduced to *cis*-6-methyl-4-N-methylaminoflavan **12b**. However all efforts to separate **10d** and **13a** proved unsuccessful. In the light of the above results as a logical approach it was hoped that the Ritter reaction involving the intermediacy of a carbonium ion under acidic conditions[24] would provide an axial amine. This was amply borne out by the results discussed below. With acetonitrile and sulphuric acid in n-dibutyl ether (standard Ritter reaction conditions[24]) **3a** furnished an amide, m.p. 206° (IR ν_{CO} = 1640; ν_{NH} = 3290 cm^{-1}) which analyzed for 4-acetamidoflavan, and the yield was improved from 8 to 86% by changing the solvent to diethyl ether. The

m.p. of the *cis* isomer **10a** is 208° and both have the same R_f value (TLC on SiO_2) in a number of (*ca* 25) solvent systems. IR spectra of the two were almost identical and the 60 MHz spectra were inconclusive due to overlap of the H-4 multiplet and H-2 quartet and these could not be simplified by D_2O exchange even after addition of Et_3N. ^{13}C-NMR spectral studies were therefore undertaken. In the case of **10a**, m.p. 208°, the C-2 carbon signal appeared at 77.1 ppm while in the compound, m.p. 206°, from the Ritter reaction it appeared at 73.9 ppm clearly showing that this is the desired *trans*-4-acetamidoflavan **13b** with the axial C-4 acetamido group causing an upfield shift of 3.2 ppm due to the heteroatom γ-gauche effect. It may be noted that the shielding of the C-4 carbon by axial OH, OAc or OMe groups by *ca* 5 ppm in cyclohexane[25,26] is reduced to 1.7–1.9 ppm in 4-hydroxyflavans,[27] to 1.2–1.7 ppm in 4-acetoxyflavans,[27] and is further decreased to 0.8–0.9 ppm in *trans*-4-acetamidoflavans **13b** and **13c**. Moreover this assignment was fully corroborated by the re-examination of the ^{1}H-NMR spectrum in DMSO-d_6 on a 90 MHz instrument. Irradiation of the amide proton doublet at δ 8.45 simplified the H-4 multiplet to a narrow double doublet (narrow triplet) at δ 5.02 (equatorial H-4, $J_{4e,3a+4e,3e}$ = 9 Hz) clearly separated from the double doublet (broad triplet) at δ 5.22 (axial H-2, $J_{2a,3a+2a,3e}$ = 18 Hz) while irradiation of the triplet at δ 5.02 collapsed the amide proton doublet at δ 8.45 to a singlet, thus confirming its stereochemistry as in **13b**. This reaction also gave an intermediate unstable compound containing S, most probably the *trans*-imino-enol sulphate **14a** which is hydrolyzed to **13b** with water. The formation of **13b** via **14a** through the intermediacy of a benzyl carbocation (S_N1 process) was supported by the fact that **13b** was also obtained from the *trans*-alcohol **4a** in high yields. Moreover **3a** and **3f** on treating with H_2SO_4 in Et_2O alone (no CH_3CN) and subsequent addition of water furnished **4a** and **4k** in high yields. Under similar conditions **3f** and **4k** with acetonitrile gave *trans*-4-acetamido-6-methylflavan **13c** providing a second pair of isomeric 4-acetamidoflavans and this appears to be a general method.

Thus at the C-4 benzyl carbon of a flavan nucleus without a substituent at C-3, when the carbocation is generated under acidic or basic conditions, the nucleophiles halide, water and nitrile approach axially while under neutral conditions the substitutions by acetamido or phthalimido group take place with inversion. Further studies are in progress.

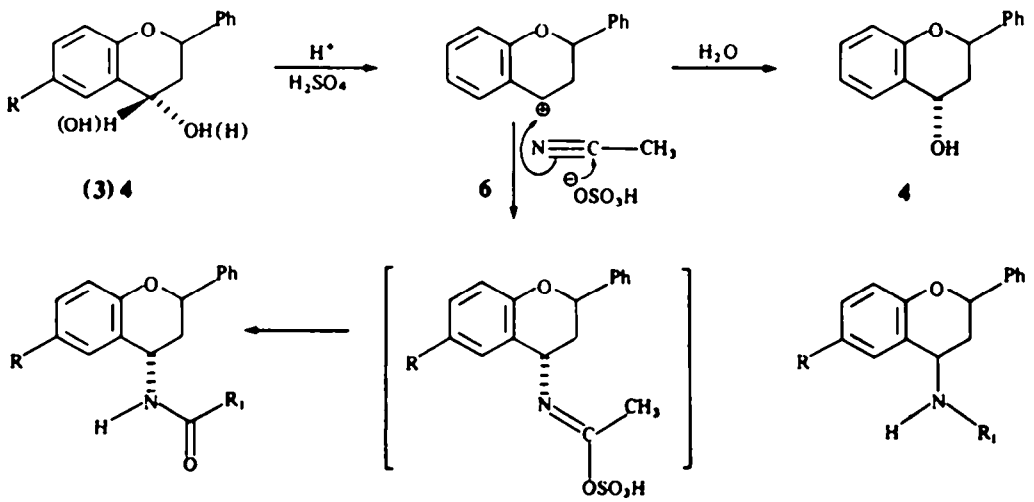
EXPERIMENTAL

M.ps were determined with a Reichert m.p. apparatus and are uncorrected. IR spectra (KBr discs) were recorded on a Perkin–Elmer 437 spectrophotometer. ^{1}H-NMR spectra were determined on Perkin–Elmer R-32 (90 MHz) or JEOL-FX-100-FT (100 MHz) NMR spectrometers using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are given in ppm from Me_4Si as internal standard. ^{13}C-NMR spectra were measured on a JEOL FX-100-FT (25.03 MHz) instrument. Merck Silica Gel G-60 (70–230 mesh) was used for chromatography.

Attempted mesylation of **3a**

(a) trans-4-*Hydroxyflavan* **4a**. Mesyl chloride (6 g, 52 mmol) in pyridine (20 ml, 250 mmol) was added slowly to a stirred soln of **3a** (2 g, 8.84 mmol) in pyridine (10 ml, 125 mmol) at 0°. After 16 hr at 0°, the mixture was poured on crushed ice and left overnight. The separated solid was collected and crystallized from light petroleum (b.p. 40–60°) to furnish **4a** (0.5 g, 25%), m.p. 117–118° (lit.[4] m.p. 118°). The benzoate (BzCl–pyridine) had m.p. 150–151° (lit.[28] m.p. 150°).

(b) trans-4-*Chloroflavan* **4d**. The mesylation mixture of the above experiment was poured on crushed ice and immediately extracted with ether, the ether layer dried (Na_2SO_4) and solvent removed *in vacuo*. The residual oil, which was solidified on cooling, was sublimed at 50°/0.65 mm to furnish **4d** (0.54 g, 25%), m.p. 53–54°. (Found: C, 73.40; H, 5.50; Cl, 14.70. $C_{15}H_{13}OCl$ requires: C, 73.60; H, 5.30; Cl, 14.50%.) Compound **4d** (0.4 g) was dissolved in pyridine (2.5 ml) and water (2 ml), and the soln left overnight at r.t. Usual work up afforded a gum. Addition of petroleum ether dissolved most of the gum leaving a small residue (5 mg, 1%) identified as **4a**. The petroleum ether soluble material was identified as flav-3-ene[9] (TLC and IR check).



Hydrolysis of **4d**

(i) *By aqueous pyridine.* A soln of **4d** (0.2 g, 0.8 mmol) in pyridine (1 ml, 12.5 mmol) and water (50 ml) was kept at room temp for 48 hr, taken up in ether, washed with HCl (5%), water, and dried (Na_2SO_4). Removal of solvent and crystallization of the product from light petroleum yielded **4a** (0.11 g, 60%), m.p. 116–117°.

(ii) *By aqueous* DMF–Li_2CO_3. DMF (5 ml), Li_2CO_3 (250 mg, 3.38 mmol) and water (3 ml) were added to **4d** (from 0.5 g, **3a** and 0.5 ml $SOCl_2$) at 0°. After 12 hr at 0° the mixture was worked up as usual to give **4a** (75%), m.p. 117°. With DMSO–Li_2CO_3–water the yield was lower (*ca* 60%).

trans-4-*Chloro-6-methylflavan* **4f**. $SOCl_2$ (5 ml) was added to **3f** (0.5 g), and after 10 min, hexane (20 ml) was added to the resulting soln. $SOCl_2$, along with hexane, was removed *in vacuo* and the residue was crystallized from hexane to give **4f** (60%), m.p. 68–69°. (Found: C, 74.56; H, 6.13. $C_{16}H_{15}OCl$ requires: C, 74.25; H, 5.80%.)

trans-4-*Bromo-6-methylflavan* **4g**. To the ice cooled soln of **3f** (1.41 g, 58 mmol) in absolute ether (75 ml) was added dropwise PBr_3 (1.58 g, 5.8 mmol) in ether (25 ml) over a period of *ca* 30 min. The soln was stirred at 0° for 5 hr, washed with NaOAc aq (35 ml, 5%) and water. The ether layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to yield an oil which solidified on trituration with light petroleum (b.p. 60–80°). Crystallization of the solid from benzene–light petroleum afforded yellow needles of **4g** (68.5%), m.p. 85°. (Found: C, 63.56; H, 5.19. $C_{16}H_{15}OBr$ requires: C, 63.36; H, 4.95%.)

Similar reaction of PBr_3 (17 g) and **3g** (15.5 g) in ether (250 ml) at 0° for 16 hr and crystallization of the product from light petroleum furnished *trans-4-bromo-4'-methoxy-6-methylflavan* **4i** (73%), m.p. 113°. (Found: C, 61.42; H, 4.90. $C_{17}H_{17}O_2Br$ requires: C, 61.26; H, 5.10%.)

trans-4,8-*Dibromo-6-methylflavan* **4j**. Bromine (0.2 ml, 3.75 mmol) in AcOH (2 ml) was added to a soln of **3f** (0.9 g, 3.74 mmol) in AcOH (2 ml) at 90°. The mixture was allowed to cool and left overnight when a solid was precipitated. Crystallization of the solid from hexane furnished **4j** (55%), m.p. 125–127°. (Found: C, 49.90; H, 3.40. $C_{16}H_{14}OBr_2$ requires: C, 50.20; H, 3.60%.)

trans-4-*Hydroxyflavans from* cis-4-*hydroxyflavans* (*via* trans-4-*chloroflavans*)

trans-4-*Hydroxy-6-methylflavan* **4k**. (i) Compound **4f** [from **3f** (50 mg) and $SOCl_2$ (0.5 ml) at 30° for 4 hr] was dissolved, without isolation, in pyridine (2.5 ml, 31.25 mmol) and water (2 ml) and the soln was allowed to stand for 16 hr at 30°. Usual work up gave **4k** (5%, 15% when the time was 24 hr at 0°), m.p. 92°. (ii) By aqueous DMSO–K_2CO_3: Compound **4f** (from 50 mg of **3f** and 0.5 ml of $SOCl_2$) was treated with DMSO (5 ml), water (3 ml) and K_2CO_3 (250 mg, 1.8 mmol) at 0° for 24 hr to give **4k** (60%), m.p. 92°. (iii) By aqueous DMF–Li_2CO_3: Compound **4f** (from 50 mg of **3f** as above) when treated with DMF (5 ml), water (3 ml) and Li_2CO_3 (250 mg, 3.38 mmol) at 0° for 24 hr gave **4k** (75%), m.p. 92°. (Found: C, 79.80; H, 6.60. $C_{16}H_{16}O_2$ requires: C, 80.00; H, 6.70%.) The acetate (Ac_2O–pyridine) had m.p. 110°. (Found: C, 76.50; H, 6.90. $C_{18}H_{18}O_3$ requires: C, 76.59; H, 6.40%.) NMR ($CDCl_3$): δ 5.16 (1H, dd, $J_{a,e}$ = 14 Hz, H-2), 5.95 (1H, dd, $J_{e,e}$ = 6 Hz, H-4).

trans - 3',4' - *Dimethoxy* - 4 - *hydroxy* - 6 - *methylflavan* **4m**. Reaction of **3h** (300 mg, 1 mmol) in $SOCl_2$ (0.5 ml, 6.88 mmol) and then with Li_2CO_3 (250 mg, 3.38 mmol) in water (3 ml) and DMF (5 ml) for 12 hr at 0° gave **4m** (75%), m.p. 136°. (Found: C, 71.55; H, 6.67. $C_{18}H_{20}O_4$ requires: C, 72.00; H, 6.66%.) Similarly the *cis*-alcohols **3i** and **3j**[29] gave trans-3',4'-*dimethoxyflavan* **4n** (70%), m.p. 113°. (Found: C, 71.13; H, 6.20. $C_{17}H_{18}O_4$ requires: C, 71.32; H, 6.29%.) and trans-4-*hydroxy*-3',4',7,8-*tetramethoxyflavan* **4o** (85%), m.p. 104°. (Found: C, 66.06; H, 6.38. $C_{19}H_{22}O_6$ requires: C, 65.89; H, 6.35%.)

Hydrolysis of trans-4-*bromoflavans*

(i) *Compound* **4e**. Compound **4e** (1 g, 3.46 mmol) was added at 0° to a soln of Li_2CO_3 (570 mg, 7.71 mmol) in DMF (10 ml) and water (6 ml) and the mixture was allowed to stand at 0° for 12 hr. Usual work up furnished **4a** (75%), m.p. 117°.

(ii) *Compound* **4g**. A soln of **4g** (0.5 g, 1.6 mmol) in DMF (3 ml), water (2 ml) and K_2CO_3 (250 mg) or Li_2CO_3 (250 mg) was stirred for 24 hr at 0°. Usual work up yielded **4k** (75–80%), m.p. 92°.

Compound **4l**. Water (2 ml) was added to a soln of **4l** (0.92 g, 2.38 mmol) in pyridine (10 ml, 125 mmol). After 24 hr at 30° the mixture was poured into ice water and solid obtained was crystallized from EtOH to furnish **4l** (37%), m.p. 135°.

Compound **4j**. Compound **4j** (250 mg, 0.65 mmol) was added to DMF (5 ml) and water (1.5 ml) containing Li_2CO_3 (125 mg, 7 mmol) and the mixture was stirred for 12 hr at r.t., poured into water, extracted with ether, washed with water and dried ($MgSO_4$). Removal of solvent *in vacuo* and crystallization of the residue from $CHCl_3$–hexane furnished trans-8-*bromo-4-hydroxy-6-methylflavan*: **4p** (77%), m.p. 90–92°. (Found: C, 60.21; H, 4.86. $C_{16}H_{15}O_2Br$ requires: C, 60.19; H, 4.64%.)

trans - 4 - *Hydroxy* - 3',4',7 - *trimethoxyflavan* **4q**. *cis*-4-Hydroxy-3',4',7-trimethoxyflavan (0.32 g, 1 mmol) was reacted with PBr_3 (0.3 ml, 0.38 mmol) in ether (10 ml) at 0° for 6 hr and poured into water. Immediate work up furnished **4q** (80%), m.p. 109°. (Found: C, 68.50; H, 6.93. $C_{18}H_{20}O_5$ requires: C, 68.36; H, 6.33%.)

Compound **4k** *via lead tetra-acetate oxidation*

(a) 6-*Methylflavan*. Zn dust (25 g, 382 mmol) was added to water (40 ml) containing $HgCl_2$ (2.5 g, 9.2 mmol), filtered after 10 min washed with water and AcOH. The resulting Zn amalgam was added to the soln of 6-methylflavanone (2.5 g, 10.5 mmol) in AcOH (10 ml) and conc HCl (10 ml) and left overnight. The mixture was diluted with water, neutralized (Na_2CO_3) and isolation with ether gave an oil which on distillation *in vacuo* furnished 6-methylflavan (89%), b.p. 150°/1.2 mm. (Found: C, 85.69; H, 7.14. $C_{16}H_{16}O$ requires: C, 85.71; H, 7.14%.)

(b) trans-4-*Acetoxy-6-methylflavan*. 6-Methylflavan (3.9 g, 17.4 mmol) in benzene (155 ml) was treated with $Pb(OAc)_4$ (7.8 g, 17.5 mmol) under reflux for 14 hr. Inorganic salts were removed by filtration and removal of solvent from the filtrate *in vacuo* furnished a residue (2.68 g) which contained starting 6-methylflavan and *trans*-4-acetoxy-6-methylflavan (TLC check). Chromatography on a column of neutral alumina with light petroleum furnished in the first fraction 6-methylflavan (2.2 g) and further elution with light petroleum–benzene (1 : 2) gave *trans*-4-acetoxy-6-methylflavan (180 mg, 9%), m.p. 110°. (Found: C, 76.50; H, 6.90. $C_{18}H_{18}O_3$ requires: C, 76.59; H, 6.40%.)

(c) *Compound* **4k**. The above acetate (142 mg, 0.5 mmol) in MeOH (25 ml) and KOH (1.44 g, 25.66 mmol) was refluxed for 3.5 hr. Usual work up furnished **4k** (60 mg, 50%), m.p. 92° (IR comparison).

Action of silver tosylate in acetonitrile on trans-4-*halogenoflavans*

cis-4-*Acetamidoflavan* **10a**. Compound **4d** (2.5 g, 10.22 mmol) or **4e** (2.9 g, 10 mmol) was added to a soln of AgOTs (3.2 g, 11.46 mmol) in acetonitrile (100 ml) at 0.5°. The mixture was protected from light and stirred at 0° for 2 hr, allowed to stand overnight, the Ag salts were filtered off and acetonitrile was removed *in vacuo*. The residue was extracted with ether, washed with water and dried (Na_2SO_4). Removal of solvent (*in vacuo*) and crystallization of the resulting solid from MeOH furnished **10a** (1.1 g, 40%), m.p. 208°. (Found: C, 76.24; H, 6.39. $C_{17}H_{17}NO_2$ requires: C, 76.40; H, 6.36%.)

Similarly **4f** and **4g** furnished **10b**, m.p. 214–216°. (Found: C, 76.71; H, 6.71. $C_{18}H_{19}NO_2$ requires: C, 76.80; H, 6.80%.) A soln of 6-methylflavanone (15.2 g, 0.064 mmol) and hydroxylamine hydrochloride (35 g, 0.5 mol) in aqueous pyridine (300 ml, 66%) was refluxed for 5 hr and poured on cold dil. HCl (1 : 1) to furnish a solid which on crystallization from MeOH gave 6-methyl-4-oximinoflavan (13 g, 80%), m.p. 188–190°. (Found: C, 75.76; H, 6.10. $C_{16}H_{15}O_2N$ requires: C, 75.93; H, 5.93%.) (ii) To a stirred suspension of $LiAlH_4$ (1 g, 25

mmol) in anhydrous ether (25 ml) was added dropwise a soln of the above oxime (1.26 g, 5 mmol) in anhydrous ether (100 ml) and THF (25 ml) and the mixture was stirred under reflux for 5 hr. The unreacted $LiAlH_4$ was destroyed by ether saturated with water; the soln was poured in dil. HCl (50 ml; 1:1) and extracted with ether. The aqueous phase was basified in the cold by NaOH (10 N), extracted with $CHCl_3$ and the $CHCl_3$ extract was dried (Na_2SO_4). Evaporation of the solvent furnished *cis*-4-amino-6-methylflavan as an oil (695 mg) which was dissolved in pyridine (2.5 ml) and treated with Ac_2O (2.5 ml). Work up after 16 hr furnished **10b** (225 mg, 15%), m.p. 215° (IR comparison).

trans-4-*Tosyloxyflavan* **4r**

(a) *Wet phase-transfer catalysis.* A soln of *p*-TsCl (2.1 g, 11 mmol) in benzene (5 ml) was added dropwise to a stirred two phase heterogeneous suspension of **4a** (2.26 g, 10 mmol), benzylcetyl-dimethylammonium chloride (160 mg), benzene (10 ml) and aqueous NaOH (5 ml, 30%) at 20–25°. The reaction was terminated after the disappearance of **4a** (TLC check) and the odour of sulphonyl chloride. The organic layer was separated, washed with water till neutral and dried (Na_2SO_4). Removal of the solvent and purification of the resulting product by chromatography (SiO_2—eluent benzene) furnished **4r** (1.2 g, 31%), m.p. 153–155°. (Found: C, 69.60; H, 5.40. $C_{22}H_{20}O_4S$ requires: C, 69.47; H, 5.26%.)

(b) *Dry phase-transfer catalysis.* To a stirred suspension of **4a** (0.6 g), NaOH (0.32 g), Na_2CO_3 (0.42 g) and cetyl-dimethylbenzyl ammonium chloride (40 mg) in benzene (5 ml) was added a soln of *p*-TsCl (0.6 g, 3.14 mmol) in benzene (5 ml) and stirring continued at 15–20° for 12 hr to complete the reaction (TLC check). The mixture was poured into water, the organic layer was washed with water till neutral, dried and solvent removed *in vacuo*. Crystallization of the residue from $CHCl_3$ furnished **4r** (65%), m.p. 153–155°. Similarly **4k** gave **4s** (40%), m.p. 186–187°. (Found: C, 70.20; H, 5.70. $C_{23}H_{22}O_4$ requires; C, 70.07; H, 5.58%.) Compound **4r** when reacted with acetonitrile was recovered unchanged.

Reaction of K-*phthalimide with* trans-4-*halogenoflavans: cis*-4-*phthalimidoflavan* **11**

To a stirred soln of phthalimide (1.45 g, 9.86 mmol) in DMF (15 ml) methanolic KOH (1.2 ml, 50%) was added at 85° when the MeOH was distilled over. The mixture was cooled to 50°, **4e** (2.9 g, 10 mmol) was added and the stirring continued. After 30 min at 50° the mixture was poured on ice water and the separated solid was collected, washed successively with water and MeOH and crystallized from MeOH to furnish **11** (1.2 g, 33.6%), m.p. 178° (lit.[6] m.p. 178°). (Found: C, 77.30; H, 4.90; N, 4.15. $C_{23}H_{17}NO_3$ requires: C, 77.73; H, 4.70; N, 3.90%.)

Reaction of sulphur and phosphorus halides on cis- *and* trans-4-*hydroxyflavans*

(i) $SOCl_2$ (2.0 ml, 27.5 mmol) was added at 0° to finely powdered **3a** (6.0 g, 8.84 mmol). After 10 min at r.t., petroleum ether (b.p. 40–60°) was added and excess $SOCl_2$ was removed (*in vacuo*). The residue was sublimed at 50°/0.6 mm to furnish **4d** as a pale yellow solid (1.5 g, 69.4%), m.p. 53–54°.

(ii) PCl_3 (1 g, 7.28 mmol) was added to a stirred suspension of **3a** (1 g, 4.42 mmol) in dry ether (20 ml) at 0°. After 5 hr at 0° the ethereal layer was washed with NaOAc (5%), water and dried (Na_2SO_4). Removal of the solvent (*in vacuo*) and crystallization of the residue from petroleum ether furnished **4d** (0.75 g, 69.5%), m.p. 54–56°.

(iii) PCl_5 (1.2 g, 5.76 mmol) was added to a stirred suspension of **3a** (1 g, 4.42 mmol) in dry ether (50 ml) at 0°, and stirring continued at 0° for 5 hr. Usual work up gave **4d** (0.6 g, 55.5%), m.p. 58°.

Compound **4a**, under similar conditions as in i, ii and iii above, furnished **4d**, m.p. 56–58° (mixed m.p., IR, ^{1}H-NMR and ^{13}C-NMR comparison).

Compound **4a** with PBr_3 in ether under conditions used for **3a**[13] furnished **4e** (77%), m.p. 85–87°. (Found: C, 62.14; H, 4.51. $C_{15}H_{13}BrO_3$ requires: C, 62.29; H, 4.50%.) (^{1}H-NMR comparison with the authentic sample.[13]) It was also obtained by $SOBr_2$ from **3a** and **4a** under conditions used for $SOCl_2$ as above (IR comparison).

Compound **4k** (0.2 g, 0.8 mmol) in ether (10 ml) with PBr_3 (0.224 g, 0.83 mmol) in ether (10 ml) at 0° for 5 hr and usual work up gave **4g** (50%), m.p. 85°, identical with the one obtained from **3f**.

cis-4-N-*Formylaminoflavan* **10e**

(i) *Leuckart reaction.* A mixture of flavanone (5 g, 22.3 mmol) in formic acid (40 ml, 90%) and formamide (41 ml) was heated in an oil bath at 180° for 3 hr with the simultaneous removal of the distillate. Dilution of the residue with cold water (50 ml) and basification with cold ammonia gave a brown solid which was crystallized from EtOH to give **10e** (1.2 g, 21%), m.p. 185–187°. (Found: C, 75.70; H, 6.10. $C_{16}H_{15}NO_2$ requires: C, 75.88; H, 5.92%.)

(ii) *Formylation. cis*-4-Aminoflavan[5,6] (450 mg, 2 mmol), fused NaOAc (2 g, 24 mmol) and formic acid (15 ml) were refluxed for 3.5 hr. Isolation with ether and crystallization of the product from EtOH furnished **10e** (0.15 g, 30%), m.p. 185–187° (IR comparison).

cis-4-N-*Methylaminoflavan* **12a**

To a stirred slurry of $LiAlH_4$ (250 mg, 6.2 mmol) in ether (25 ml) was added a soln of **10e** (253 mg, 1 mmol) in THF (10 ml) and the mixture refluxed for 72 hr. Isolation with ether and crystallization from $CHCl_3$–hexane gave **12a** (985 mg, 35%), m.p. 56°. (Found: C, 80.60; H, 7.40%. $C_{16}H_{17}NO$ requires: C, 80.33; H, 7.11%.)

Leuckart reaction with 6-methylflavanone (5.31 g, 22.3 mmol), formic acid (40 ml, 90%) and formamide (41 ml) as above furnished a mixture of **10d** and **13a** (1.02 g, 17%), m.p. 182–183°.

Formylation of *cis*-4-amino-6-methylflavan (0.239 g, 1 mmol) with fused NaOAc (1 g, 12 mmol) and formic acid (7.5 ml, 90%) furnished **10d** (85 mg, 31.8%), m.p. 188–189°. (Found: C, 76.61; H, 6.34; N, 4.88. $C_{17}H_{17}NO_2$ requires: C, 76.40; H, 6.36; N, 5.24%.) This was indistinguishable from the above mixture by TLC (24 solvent combinations) and $LiAlH_4$ reduction as above furnished **12b**, m.p. 77°. (Found: C, 80.40; H, 7.60; N, 5.26. $C_{17}H_{19}NO$ requires: C, 80.63; H, 7.40; N, 5.53%.)

Ritter reaction on **3a** *and* **4a**: trans-4-*acetamidoflavan* **13b**

(a) To a stirred soln of **3a** or **4a** (226 mg, 1 mmol) in n-dibutyl ether (15 ml) and acetonitrile (0.2 ml, 3.8 mmol) was added conc H_2SO_4 (1 ml) in n-dibutyl ether (10 ml) at 50°. After 1 hr at 40–50°, the mixture was poured into water. Isolation with ether and crystallization of the product from light petroleum furnished **13b** (140 mg, 55%), m.p. 206°. (Found: C, 76.28; H, 6.90; N, 5.10. $C_{17}H_{17}NO_2$ requires: C, 76.40; H, 6.36, N, 5.24%.) (b) To a soln of **3a** or **4a** (226 mg, 1 mmol) in ether (10 ml) and acetonitrile (5 ml) was added at 0° a soln of conc H_2SO_4 (1 ml) in ether (10 ml). Work up after 24 hr at r.t. gave **13b** (85%), m.p. 206°.

Similarly **3f** and **4k** gave **13c**, m.p. 195–196°. (Found: C, 76.52; H, 7.11; N, 4.48. $C_{16}H_{19}NO_2$ requires: C, 76.84; H, 6.76; N, 4.90%.)

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